Claims

1. A pharmaceutical composition comprising crizanlizumab that has light chain and heavy chain amino acid sequences in SEQ ID NO: 10 and SEQ ID NO: 9 respectively, and a variant of crizanlizumab (iso-crizanlizumab), in which amino acid aspartic acid at position 32 of SEQ ID NO: 10 is changed to iso-aspartic acid.

2. The pharmaceutical composition of claim 1 further comprising succinimide of crizanlizumab at position 32 of SEQ ID NO: 10.

3. The pharmaceutical composition of claim 1 or 2, wherein the iso-crizanlizumab consists of homo-iso-crizanlizumab and hetero-iso-crizanlizumab.

4. The pharmaceutical composition of any one of the claims 1 to 3 comprising ~~at least 20% crizanlizumab of the total charge variants in the pharmaceutical composition.~~

~~5. The pharmaceutical composition of any one of the claims 1 to 4 comprising at most 50% crizanlizumab of the total charge variants in the pharmaceutical composition.~~

~~6. The pharmaceutical composition of any one of the claims 1 to 5 comprising~~ from about 20% to about 50% crizanlizumab of the total charge variants in the pharmaceutical composition.

~~7~~5. The pharmaceutical composition of any one of the preceding claims further comprising a buffer system, wherein the composition has a pH from about 5.5 to about 7.5.

~~8~~6. The pharmaceutical composition of claim ~~7~~5, wherein the pH is about 5.5 to about 7, preferably about 5.5 to about 6.5, preferably about 5.7 to about 6.3~~.~~, preferably the pH is about 5.9 to about 6.1.

~~9~~7. The pharmaceutical composition of claim 7 or ~~8, wherein the pH is about 5.9 to about~~ claim 6~~.1.~~

~~10. The pharmaceutical composition of any one of claims the 7-9~~, wherein the buffer system is citrate buffer~~.~~

~~11. The pharmaceutical composition of any one of the claims 7-9, wherein the buffer system is~~ phosphate buffer.

~~12~~8. The pharmaceutical composition of any one of the preceding claims further comprising a stabilizer~~.~~

~~13. The pharmaceutical composition of claim 12, wherein~~ , preferably the stabilizer is sucrose~~.~~

~~14. The pharmaceutical composition of claim 13, wherein~~, preferably sucrose is in a concentration of 50 mM to 350 mM, preferably 100 mM to 300 mM.

~~15~~9. The pharmaceutical composition of any one of the preceding claims further comprising an isotonizing agent, preferably the isotonizing agent is sodium chloride, preferably sodium chloride is in a concentration of 50 mM to 300 mM.

~~16. The pharmaceutical composition of claim 15, wherein the isotonizing agent is sodium chloride.~~

~~17. The pharmaceutical composition of claim 16, wherein sodium chloride is in a concentration of 50 mM to 300 mM.~~

~~18~~10. The pharmaceutical composition of any one of the preceding claims further comprising a surfactant~~.~~

~~19. The pharmaceutical composition of claim 18, wherein~~ , preferably the surfactant is a non-ionic surfactant~~.~~

~~20. The pharmaceutical composition of claim 18 or 19, wherein~~, preferably the surfactant is polysorbate, preferably polysorbate 80~~.~~

~~21. The pharmaceutical composition of any of the claims 18 to 20, wherein~~, preferably the surfactant, preferably polysorbate, is in a concentration of 0.01% w/v (0.1 mg/mL) to 0.1% w/v (1 mg/mL).

~~22~~11. The pharmaceutical composition of any one of the preceding claims, ~~wherein ANTIBODY is~~comprising antibody in a concentration from 5 mg/ml to 50 mg/ml.

~~23~~12. A pharmaceutical composition comprising antibody in a concentration from about 5 to about 50 mg/ml, and a buffer system, wherein the composition has a pH from about 5.5 to about 7.5, preferably the pH is about 5.7 to about 6.3.

~~24~~13. The pharmaceutical composition according to claim ~~23, wherein the pH is about 5.7 to about 6.3.~~

~~25. The pharmaceutical composition according to claim 23 or 24~~12, wherein the buffer system is citrate (e.g. sodium citrate) and/or phosphate (e.g. potassium phosphate).

~~26. The pharmaceutical composition according to any one of the claims 23-25 further comprising a stabilizer.~~

~~27~~14. The pharmaceutical composition according to claim ~~26, wherein~~12 or claim 13 further comprising a stabilizer, preferably the stabilizer is sucrose~~.~~

~~28. The pharmaceutical composition according to claim 26 or 27, wherein~~, preferably the stabilizer is present in a concentration of about 50 mM to about 300 mM.

~~29~~15. The pharmaceutical composition according to any one of the claims ~~23-28~~12 to 14 further comprising a non-ionic surfactant~~.~~

~~30. The pharmaceutical composition according to claim 29, wherein~~, preferably the surfactant is polysorbate 80~~.~~

~~31. The pharmaceutical composition according to claim 29 or 30, wherein~~, preferably the surfactant, preferably polysorbate 80, is present in a concentration of about 0.01% w/v (0.1 mg/ml) to 0.1% w/v (1 mg/ml).

~~32~~16. The pharmaceutical composition according to any one of the claims ~~23-31~~12 to 15 further comprising an isotonizing agent~~.~~

~~33. The pharmaceutical composition according to claim 32, wherein~~, preferably the isotonizing agent is NaCl~~.~~

~~34. The pharmaceutical composition according to claim 32 or 33, wherein~~, preferably the isotonizing agent, preferably NaCl is present in a concentration of about 50 mM to 300 mM.

~~35~~17. A pharmaceutical composition comprising antibody (crizanlizumab and any variants thereof) in a concentration from about 5 to about 50 mg/ml, sucrose in a concentration of about 50 mM to about 350mM, and a buffer system, wherein the composition has a pH from about 5.5 to about 7.5, preferably about 5.7 to about 6.3, e.g. about 6.0, and wherein the buffer system is citrate buffer and/or phosphate buffer.

~~36. The pharmaceutical composition according to claim 35, wherein the pH of the pharmaceutical composition is about 5.7 to about 6.3, e.g. about 6.0.~~

~~37~~

18. The pharmaceutical composition according to any one of the preceding claims in a lyophilized form.

~~38. A lyophilized formulation obtainable by lyophilizing an aqueous formulation, wherein the lyophilized formulation comprises:~~

~~a) antibody (crizanlizumab and any variants thereof);~~

~~b) a lyoprotectant; and~~

~~c) a buffer system.~~

~~39. The lyophilized formulation of claim 38 further comprising a surfactant.~~

~~40. The lyophilized formulation of claim 39, wherein said surfactant is polysorbate 80.~~

~~41. The lyophilized formulation of any one of the claims 38-40, wherein antibody is present in the aqueous formulation in a concentration of about 10 mg/mL to 100 mg/mL.~~

~~42. The lyophilized formulation of any one of the claims 38-41, wherein the buffer system is citrate, e.g. sodium citrate.~~

~~43. The lyophilized formulation of any one of the claims 38-42 further comprising sucrose and/or mannitol as lyoprotectant.~~

~~44. The lyophilized formulation of any of claims 38-43, wherein said aqueous formulation comprises sucrose in a concentration of about 10 mg/mL to 100 mg/mL.~~

~~45. The lyophilized formulation of any of claims 43-44, wherein the molar ratio of sucrose to antibody is from about 200 to 1500.~~

~~46. The lyophilized formulation of any of claims 38-45 comprising~~
~~a) about 25 - 40 w/w %, preferably about 28 to 32 w/w% , of antibody; and~~
~~b) about 55 - 75 w/w %, preferably about 65 to 71 w/w % of sucrose,~~
~~based on the total weight of the lyophilized formulation.~~

~~47. A liquid pharmaceutical composition obtained by reconstituting the lyophilized formulation of any one of the claims 37 to 46.~~

~~48~~19. The pharmaceutical composition according to any one of the preceding claims, wherein the IC50 determined by using the pharmaceutical composition is in the range of about 4.6-6.2 µg/ml~~.~~, the IC50 is determined in vitro.

~~49~~20. The pharmaceutical composition according to ~~claim 48, wherein the IC50 is determined~~any one of claims 1-19 for use in ~~vitro.~~

~~50. A~~a method of treating sickle cell disease, especially preventing Vascular Occlusion Crises (VOC) in a subject in need thereof ~~comprising administering~~, wherein a therapeutically effective dose of antibody (crizanlizumab and any variants thereof) ~~comprised in the pharmaceutical composition according~~is to ~~any one of the claims 1-47~~be administered to subject, wherein the therapeutically effective dose is 5mg or 7.5mg per kilogram of the body weight of subject, wherein

preferably the first 2 doses are to be administered 2 weeks apart, followed by administration of the same dose every four weeks, preferably the pharmaceutical composition is to be administered to a subject by intravenous route.

~~51. The method according to claim 50, wherein the first 2 doses are administered 2 weeks apart, followed by administration of the same dose every four weeks.~~

~~52. The method of claim 50 or 51, wherein the pharmaceutical composition is administered to a subject by intravenous route.~~

~~53. The method of any one of the claims 50 to 52, wherein the therapeutically effective dose is 5mg per kilogram of the weight of subject, wherein the first 2 doses are administered 2 weeks apart, followed by administration of the same dose every four weeks, and wherein one or more or all of the following PK parameters are met:~~

~~a) a t_{max} in a range for from 0.4 to 10 hours (h), preferably from 0.55 h to 6.25 h, with a preferred Median of 1.5 to 2.5 h, preferably of 1.92 h, after administrationof said pharmaceutical composition;~~

~~b) a C_{max} in the range of, after first dose , 116 ± 91.3 µg/mL; or preferably at steady state at 50 to 200 µg/mL, preferably at 124 ± 31.6 µg/mL;~~

~~c) an apparent $t_{1/2}$ in the range of 100 h to 300 h, preferably in the range of 150 h to 210 h, e.g. at about 183 h (7.6 days);~~

~~d) an $AUC_{tau, ss}$ in the range of 10 000 to 30 000 µg × h/mL, preferably at week 15 at 20400 µg × h/mL, preferably with a Coefficient of Variance of 23.5 %;~~

~~e) a mean clearance at steady state week 15, preferably in a patient with SCD and a body weight of 70 kg, in the range of 10 to 30 mL/h, preferably 15 to 20 mL/h, e.g. at about 17.2 mL/h;~~

~~f) a PK trough concentration obtained every 4 weeks in the steady state, especially from week 7 to week 27, range from about 3.78 µg/mL to 9.8 µg/mL.~~

~~54. The method of any one of the claims 50 to 52, wherein crizanlizumab and any variants thereof in serum achieves at least 70%, at least 80%, at least 90%, at least 95% inhibition of binding of P-Selectin with PSGL-1.~~